Regarding the Amendments

Claims 13, 14, 21, 24 and 25 have been amended to indicate that the recited peptide "exhibits at least two-fold greater specific binding to brain than to kidney." The amendment is supported in the specification, for example, at page 15, lines 5-12, which indicates that selective homing is characterized by at least a two-fold (2x) greater specific binding of a homing molecule to the selected organ as compared to a control organ. The amendment further is supported at page 33, lines 9-11, which indicates that kidney was used as the control organ for *in vivo* panning with brain as the selected organ, and at page 37, lines 1-9, which indicates that the ratio of selective homing (brain: kidney) for the SRL-containing peptides SEQ ID NO: 1 and SEQ ID NO: 3 was about 8 and that the ratio of selective homing (brain: kidney) for the VLR-containing peptide SEQ ID NO: 16 was about 9.

Claims 15, 17 and 19 have been amended to independent form and are directed to a peptide that selectively homes to brain and contains the amino acid sequence SEQ ID NO: 3, SEQ ID NO: 1 or SEQ ID NO: 19, respectively. Amended claims 15, 17 and 19 are supported in the specification, for example, at page 36, Table 1, which discloses the sequences of peptides SEQ ID NOS: 1, 3 and 5, which were identified based on their brain homing properties. Amended claims 15, 17 and 19 also are supported in the specification, for example, at page 11, line 27, to page 12, line 3, which indicates that a homing peptide can be expressed as a fusion protein (see, also, page 31, lines 20-25),

and at page 24, lines 25-32, which indicates that an organ homing molecule such as a brain homing peptide can be linked to a toxin such as ricin.

Regarding the Restriction Requirement

Applicants respectfully traverse the Restriction Requirement for the reasons of record and request that, upon an indication of allowable subject matter, the conjugate claims be rejoined with the peptide claims. While the claimed conjugates are patentably distinct from the claimed conjugates, that they share the recited property of selectively homing to brain and of exhibiting at least two-fold greater specific binding to brain than to kidney. In addition, Applicants respectfully submit that, where conjugates are derived from peptides which are patentable over the prior art, the conjugates themselves necessarily will be patentable over the prior art.

In view of the above remarks, it is respectfully requested that the Examiner reconsider rejoining the conjugate claims (claims 13, 21 to 23 and 25 to 27) to the claims under examination upon an indication of allowable subject matter.

Regarding the Rejection of claims 14 to 20, 24 and 28 to 41 under 35 U.S.C. § 112, first paragraph

The rejection of claims 14 to 20, 24 and 28 to 41 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement respectfully is traversed. The rejection is based, in part, on

the lack of competition experiments to confirm the specificity of homing. Furthermore, the Office Action indicates that the binding is only measured with respect to a single organ other than brain (kidney) and asserts that "selective homing" indicates that a peptide is more abundant in that organ than in any other control organ.

Applicants maintain that the full scope of the claims is enabled for the reasons of record and as set forth below.

Regarding peptide competition experiments

The Office Action states that "in order to confirm the specificity of a peptide for directing homing to a selected organ, peptide competition experiments were performed." Applicants respectfully submit that the Examiner has misinterpreted this statement.

Applicants assert that competition experiments are not necessary to demonstrate "selective homing." As acknowledged in the Office Action, the subject application discloses the use of competition experiments with a homing peptide. The results corroborated the specificity of the homing and confirmed that homing was a consequence of the peptide displayed on the phage rather than the phage itself. For example, the subject application discloses that the synthetic cyclic brain homing peptide, CLSSRLDAC (SEQ ID NO: 3), inhibited homing of phage expressing the same sequence by about 60%. The specification indicates that these results show that the brain homing of phage

bearing SEQ ID NO: 3 is specifically due to the presence of peptide SEQ ID NO: 3, rather than to some other element of the phage. See, for example, page 39, lines 20-23, which states that "This result demonstrates that the homing of the phage to brain is specifically due to the expression on the phage of the CLSSRLDAC (SEQ ID NO: 3) peptide. Thus, the competition experiments were done to confirm the importance of the peptide component.

Furthermore, as discussed with the Examiner in the recent telephonic interview, the lack of competition of peptide CENWWGDVC (SEQ ID NO: 2) by CLSSRLDAC (SEQ ID NO: 3) does not indicate a lack of specificity. One of the advantages of the homing technology is that the target molecules within brain to which the homing molecules bind are not defined or restricted to a single molecule. Rather, through the *in vivo* panning methods, homing molecules are identified that can specifically bind an assortment of target molecules present in brain, broadening the types of homing molecules that are isolated. Given the basis for how the brain homing peptides of the invention were identified, it is not at all surprising that distinct homing peptides bound different target molecules. That this is the case is supported by the failure of the brain homing peptide SEQ ID NO: 3 to inhibit brain homing of phage bearing the brain homing peptide SEQ ID NO: 2. As indicated in the specification, the lack of competition indicates that the CENWWGDVC (SEQ ID NO: 2) peptide recognizes a different target molecule than SEQ ID NO: 3 (page 39, lines 24-32). Again, this lack of competition by an

(page 39, lines 24-32). Again, this lack of competition by an unrelated peptide does not indicate a lack of specificity.

Regarding the definition of "selective homing"

The present invention is directed to peptides that "selectively home" to the selected organ, brain. As defined in the specification, a molecule that "selectively homes" to an organ binds relatively specifically to a target molecule present in one or a few selected organs (page 15, 5-9). As further defined in the specification, a molecule that "selectively homes" generally is characterized by at least a two-fold greater specific binding of the molecule to the selected organ as compared to a control organ (page 15, lines 9-12). For example, the brain homing peptides disclosed in the subject application were identified based on the enrichment of their sequences in brain as compared to the control organ, kidney. See, for example, Example IIA, which indicates that when brain was the selected organ, phage were recovered from brain and from kidney and the number of transducing units was compared. As indicated in Example IIA, 6 times more $CX_{5-7}C/CX_9$ phage bound to brain than to kidney in the second round of panning, and 13 times $CX_{5-7}C/CX_9$ phage bound to brain than to kidney in the third round (page 33, line 27, to page 34, line 3). Similarly, the enrichment ratio of individual phage recovered from the selected organ, brain, was compared to kidney for SEQ ID NO: 1, 2, 16 and 3, and in each case the enrichment ratio indicated that there was selective homing (page 35, lines 3-15). Specifically, an 8-fold ratio of brain to kidney binding was seen for the SRL-containing peptides

CNSRLHLRC (SEQ ID NO: 1) and CLSSRLDAC (SEQ ID NO: 3); a 9-fold ratio of brain to kidney homing was seen for the VLR-containing peptide, WRCVLREGPAGGCAWFNRHRL (SEQ ID NO: 16), and a 4-fold ratio of brain to kidney homing was seen for CENWWGDVC (SEQ ID NO: 2; page 37, lines 1-9). Thus, each of the brain homing peptides isolated were characterized by at least two-fold greater specific binding to brain than to kidney. In order to more clearly indicate that each of the claimed peptides that selectively homes to brain has this property of specific binding, claims 14 and 24 have been amended to indicate that the claimed peptide "exhibits at least two-fold greater specific binding to brain than to kidney."

Applicants point out that a peptide of the invention that selectively homes to brain also can home to one or a few other organs. As set forth in the specification, a molecule that "selectively homes" binds relatively specifically to a target molecule present in one or a few selected organs (page 15, 5-9). Given that the claimed brain homing molecules exhibit at least a 2-fold greater specific binding to brain than to the control organ, kidney, it is clear to the skilled person that the claimed peptides can bind to one or a few organs in addition to brain, provided that the molecule binds with at least a 2-fold greater specific binding to brain than to kidney.

In view of the above remarks and claim amendments, Applicants submit that the full scope of the claims is enabled and respectfully request that the rejection under 35 U.S.C. § 112, first paragraph, be removed.

III. CONCLUSION

In light of the amendments and remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, she is invited to call the undersigned agent or Cathryn Campbell.

Respectfully submitted,

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